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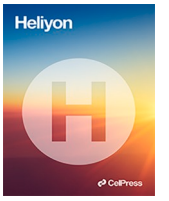

Research article

# EBNA-1 antibody and autoimmune rheumatic diseases: A Mendelian Randomization Study

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ABSTRACT

*Background:* Numerous studies have investigated a possible correlation between Epstein-Barr virus (EBV) and autoimmune rheumatic diseases (ARDs). However, establishing a cause-and-effect relationship remains a challenging endeavor. This study employs Mendelian randomization to examine the impact of EBV nuclear antigen-1 antibody (EBNA-1) antibody levels on the susceptibility to nine distinct ARDs, including rheumatoid arthritis (RA), primary Sjogren's syndrome (PSS), systemic lupus erythematosus (SLE), undifferentiated reactive arthritis (UA), systemic sclerosis (SSc), adult-onset Still's disease (AOSD), psoriatic arthritis (PsA), dermatomyositis (DM), and ankylosing spondylitis (AS).

*Methods:* The researchers applied a two-sample Mendelian randomization approach, utilizing online data from separate cohorts of European descent. We drew upon data from GWAS related to EBNA-1 antibody levels and the nine autoimmune-related disorders. Our primary analyses predominantly relied on the Inverse Variance Weighted methodology, complemented by a range of sensitivity assessments.

*Results:* Our analysis revealed significant direct associations between EBNA-1 antibody levels and the risk of developing PSS (95 % CI: 0.44 to 0.85, $p = 0.003$), PsA (95 % CI: 0.36 to 0.99, $p = 0.044$), AS (95 % CI: 0.07 to 0.88, $p = 0.031$), and UA (95 % CI: 0.56 to 0.96, $p = 0.025$). These results remained consistent through comprehensive sensitivity analyses. However, no clear associations were found for the other specified conditions.

*Conclusions:* Our findings provide compelling evidence that EBNA-1 antibody levels play a role in developing ARDs. These findings enhance our understanding of ARD pathogenesis and hold substantial promise for developing potential treatment strategies.

## Key messages

1. The EBNA-1 antibody levels exhibit a robust correlation with the susceptibility to Sjogren's syndrome, undifferentiated reactive arthritis, psoriatic arthritis, and ankylosing spondylitis, whereas they are not correlated with other prevalent autoimmune rheumatic diseases.

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2. Our findings based on genetic analysis suggest that Epstein-Barr virus infection appears to be a promising target for developing new interventions for autoimmune rheumatic diseases, especially Sjogren's syndrome, undifferentiated reactive arthritis, psoriatic arthritis, and ankylosing spondylitis.

## 1. Introduction

Autoimmune rheumatic diseases (ARDs) are characterized by a disruption in immune tolerance causing damage to the body's tissues due to attacks on self-antigens. Despite these diseases impose significant physical and emotional distress on affected individuals and their families, their etiology and pathogenesis are not fully understood [1]. The role of the Epstein-Barr virus (EBV) in ARDs is significant, influencing immune responses and disease progression [2]. Moreover, elevated levels of EBV nuclear antigen-1 (EBNA-1) were associated with various ARDs [3–5]. However, discrepancies among studies and small sample sizes make it difficult to definitively establish a causal relationship between EBNA-1 levels and ARDs.

Mendelian randomization (MR) offers a novel approach to establish causality by using single-nucleotide polymorphisms (SNPs) identified in genome-wide association studies (GWAS) as instruments to examine the impacts of exposures[6.7], like EBNA-1 antibody levels, on outcomes such as Sjogren's syndrome risk. MR studies benefit from the random assortment of genetic variants at conception making them less susceptible to reverse causation and confounding compared to conventional observational investigations [8].

This study investigated the association between genetic variations predicted to influence blood levels of EBV antibodies and the risk of developing specific ARDs. We focused on eight ARDs that have been previously linked to EBNA-1 antibody levels.

## 2. Materials & methods

1. GWAS data on exposure factors

To establish instrumental variables (IVs), we selected genetic variants associated with EBNA-1 antibody levels from the publication of Butler-Laporte G, sourced from the European Bioinformatics Institute. This dataset comprises 9,170,056 genetic markers [6].

2. SNP selection

We included independent SNPs (with $r^2 < 0.001$ within 10,000 kb windows) exhibiting robust associations ($p \leq 5 \times 10^{-8}$) with EBNA-1 antibody blood levels.

3. Outcome data

We collected trait data from the IEU Open GWAS project and compiled a summarized dataset related to ARDs (https://gwas.mrcieu.ac.uk/datasets/). After removing duplicate studies, we included data for systemic lupus (SLE; 538 cases, 213145 controls), rheumatoid arthritis (RA; 538 cases, 213145 controls), primary Sjogren's syndrome (SS; 1290 cases, 213145 controls), psoriatic arthritis (PsA; 1455 cases, 217337 controls), systemic sclerosis (SSc; 107 cases, 218499 controls), dermatomyositis (DM; 208 cases, 213145 controls), adult-onset Still's disease (AODS; 1486 cases, 359708 controls), undifferentiated reactive arthritis (UA; 971 cases, 217683 controls), and ankylosing spondylitis (AS; 599 cases, 217431 controls). Further details are available in Table 1. Utilizing openly accessible summary data did not necessitate supplementary ethical approval.

4. MR analysis

Our study employed MR to reveal the relationship between EBNA-1 levels and ARDs. For characteristics with multiple IVs, we employed three widely utilized MR methods: the Inverse Variance Weighted (IVW) approach [9,10], weighted mode [11], and MR-Egger regression [12]. Primary results, based on more than one IV, primarily relied on IVW, with the other techniques serving as

**Table 1**
General characteristics of GWAS data.

| Factor | Year | GWAS | Population | N(cases) | N(controls) |
|---|---|---|---|---|---|
| EBNA-1ab levels | 2020 | EBI | European | 7972 | 9170056 |
| SLE | 2021 | Finn | European | 538 | 213145 |
| RA | 2010 | EBI | European | 5539 | 20169 |
| PSS | 2021 | finn | European | 1290 | 213145 |
| PSA | 2021 | finn | European | 1455 | 217337 |
| SSc | 2021 | finn | European | 107 | 218499 |
| DM | 2021 | finn | European | 208 | 213145 |
| AODS | 2021 | ukb | European | 1486 | 359708 |
| URA | 2021 | finn | European | 971 | 217683 |
| AS | 2021 | finn | European | 599 | 217431 |

supplementary analyses. We assessed the robustness of our findings using several sensitivity assessments. An additional analytical approach included a leave-one-out investigation to pinpoint any individual SNP potentially influencing the causal link. This method compares the variance that the IVs account for in both the exposure and the outcome. When the IVs account for a greater variance in the exposure variable than in the outcome variable, it strengthens the evidence supporting the identified causal relationship [13]. Furthermore, we computed F statistics to assess susceptibility to bias arising from weak instruments [14]. An F-value below 10 indicated a weak instrument, prompting its removal from the analysis.

5. Heterogeneity Evaluation

We employed Cochran's Q statistic from the two-sample MR toolkit to evaluate heterogeneity among the variables. A Q statistic surpassing the number of instruments minus one indicates heterogeneity, while a statistically significant Q statistic with a p-value below 0.05 suggests the presence of heterogeneity [15,16].

## 3. Results

After stringent quality control procedures, we identified 3–5 SNPs meeting the genome-wide statistical significance threshold ($p < 5 \times 10^{-8}$) as IVs. The F-statistics for these IVs consistently ranged from 30 to 150, indicating no susceptibility to weak instrument bias. Furthermore, our analysis did not reveal any evidence of pleiotropic effects ($p > 0.05$), and the MR-Egger regression analysis did not detect horizontal pleiotropy ($p > 0.05$).

Among the IVs ($p < 5 \times 10^{-8}$), we observed a notable correlation between EBNA-1 antibody levels and the risk degree of SS, UA, PsA, and AS. A one standard deviation increase in EBNA-1 antibody blood levels was associated with an odd ratio.

(OR) of 0.61 for SS (95 % confidence interval [CI]: 0.44–0.85, $p = 0.003$) ( Fig. 2c ) , 0.60 for PsA (95 % CI: 0.36–0.99, $p = 0.044$) ( Fig. 2d ) , 0.25 for AS (95 % CI: 0.07–0.88, $p = 0.31$) ( Fig. 2g ) , and 0.73 for UA (95 % CI: 0.56–0.96, $p = 0.025$) ( Fig. 2i ) . These findings remained robust across extensive sensitivity analyses. However, no substantial association was observed between EBNA-1 levels and other ARDs (Fig. 2ab e.f.h).In sensitivity analyses focusing on the relationships between SS, UA, PsA, AS, and EBNA-1 antibody levels, MR-Egger, weighted mode, and weighted median methods consistently produced causal estimates in terms of magnitude and direction (as shown in Table 2). Furthermore, MR-Egger regression intercept analysis found no evidence of horizontal pleiotropy ($p > 0.05$). Except for RA, PsA, AOSD, and AS, Cochrane Q statistics showed no heterogeneity ($p > 0.05$). Leave-one-out analysis identified SNPs potentially influencing the causal signal (as illustrated in Figs. 1 and 3A-I).

Fig. 1 displays a series of scatter plots that depict the Mendelian Randomization (MR) study of the impact of Epstein-Barr Virus (EBV) EBNA-1 antibody levels on the likelihood of different autoimmune disorders. The figure is divided into nine panels, with each panel representing a distinct disease, such as ( 1 ) Systemic Lupus Erythematosus (SLE), ( 2 ) Rheumatoid Arthritis (RA), ( 3 ) Primary Sjögren's Syndrome (PSS), ( 4 ) Psoriatic Arthritis (PSA), ( 5 ) Systemic Sclerosis (SSc), ( 6 ) Dermatomyositis (DM), ( 7 ) Ankylosing Spondylitis (AS), ( 8 ) Adult Onset Still's Disease (AOSD), and ( 9 ) Urticaria (UA). Each map employs three MR methods:

**Table 2**
MR analysis results between EBNA-1 antbody level with ARDs.

| Exposure | Outcome | Method | nsnp | β | Pval | Q_pval | Pleiotropy |
|---|---|---|---|---|---|---|---|
| EBNA-1 Ab | SLE | IVW | 5 | −0.427 | 0.153 | 0.051 | 0.569 |
| | | Weighted median | 5 | −0.487 | 0.062 | | |
| | | MR Egger | 5 | −0.827 | 0.426 | 0.040 | |
| | RA | IVW | 3 | −2.408 | 0.124 | 0.000 | 0.562 |
| | | Weighted median | 3 | −0.562 | 0.102 | | |
| | | MR Egger | 3 | −6.152 | 0.073 | 0.000 | |
| | SS | IVW | 5 | −0.500 | 0.003* | 0.081 | 0.248 |
| | | Weighted median | 5 | −0.520 | 0.007 | | |
| | | MR Egger | 5 | −0.952 | 0.085 | 0.176 | |
| | PSA | IVW | 5 | −0.512 | 0.044* | 0.000 | 0.196 |
| | | Weighted median | 5 | −0.502 | 0.008 | | |
| | | MR Egger | 5 | −1.260 | 0.208 | 0.014 | |
| | SSc | IVW | 5 | −0.733 | 0.074 | 0.833 | 0.424 |
| | | Weighted median | 5 | −0.680 | 0.109 | | |
| | | MR Egger | 5 | −1.530 | 0.676 | 0.983 | |
| | DM | IVW | 5 | 0.165 | 0.611 | 0.280 | 0.515 |
| | | Weighted median | 5 | −0.079 | 0.772 | | |
| | | MR Egger | 5 | −0.372 | 0.338 | 0.231 | |
| | AOSD | IVW | 5 | −0.004 | 0.115 | 0 | 0.598 |
| | | Weighted median | 5 | −0.003 | 0.004 | | |
| | | MR Egger | 5 | −0.007 | 0.430 | 0 | |
| | AS | IVW | 5 | −1.399 | 0.031* | 0 | 0.917 |
| | | Weighted median | 5 | −1.369 | 0.004 | | |
| | | MR Egger | 5 | −1.576 | 0.639 | 0 | |
| | UA | IVW | 5 | 0.140 | 0.025* | 0.381 | 0.742 |
| | | Weighted median | 5 | 0.152 | 0.168 | | |

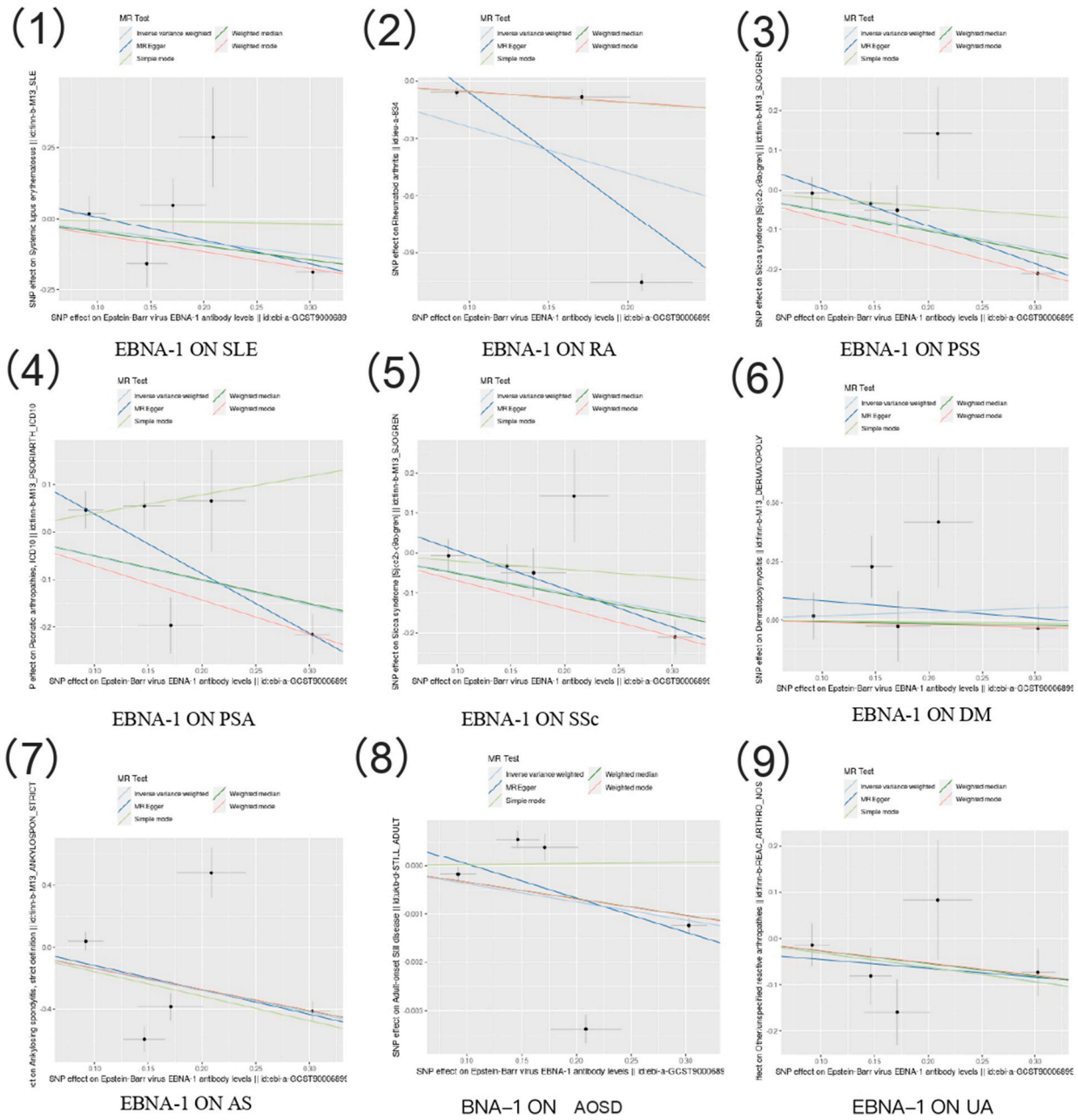


**Fig. 1.** Scatter plot of MR Causality.

Inverse Variance Weighted (IVW), Weighted Median, and Simple Mode, to estimate the causal influence. The plots include beta coefficients and confidence intervals to emphasize the diversity and importance of the results. This comprehensive visualization facilitates the evaluation of the potential cause-and-effect connections between EBNA-1 levels and susceptibility to autoimmune diseases.

Fig. 2 illustrates a set of forest plots that show the causal impact of Epstein-Barr Virus (EBV) EBNA-1 antibody levels on different autoimmune disorders, using Mendelian Randomization (MR) techniques. The plots display the odds ratios (ORs), confidence intervals (CIs), and p-values for the impact of EBNA-1 on various diseases, including(a) Systemic Lupus Erythematosus (SLE), (b) Rheumatoid Arthritis (RA), (c) Primary Sjögren's Syndrome (PSS), (d) Psoriatic Arthritis (PSA), (e) Systemic Sclerosis (SSc), (f) Dermatomyositis (DM), (g) Ankylosing Spondylitis (AS), (h) Adult Onset Still's Disease (AOSD), and (i) Urticaria (UA). The MR approaches demonstrated comprise Inverse Variance Weighted, Weighted Median, and Simple Mode, providing a resilient examination of the data. This configuration enables a distinct evaluation of the influence of EBNA-1 under various circumstances, emphasizing noteworthy discoveries and presenting statistical proof of the antibody's involvement in these ailments.

Fig. 3 displays a set of leave-one-out plots for the Mendelian Randomization (MR) analysis, which assesses the strength of the causal

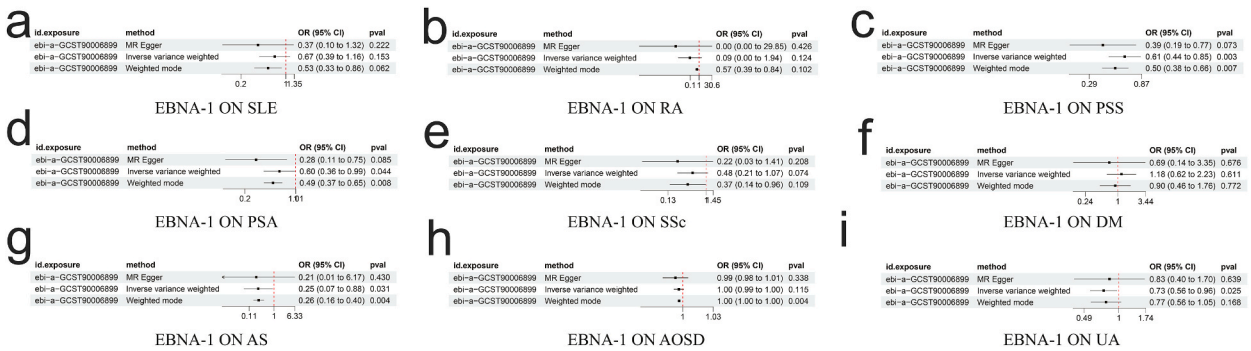


**Fig. 2.** Forest plot of MR Causality.

relationship between Epstein-Barr Virus (EBV) EBNA-1 antibody levels and several autoimmune disorders. Each plot represents a distinct disease, such as (A) Systemic Lupus Erythematosus (SLE), (B) Rheumatoid Arthritis (RA), (C) Primary Sjögren's Syndrome (PSS), (D)Psoriatic Arthritis (PSA),(E)Systemic Sclerosis (SSc), (F) Dermatomyositis (DM), (G) Ankylosing Spondylitis (AS), (H) Adult Onset Still's Disease (AOSD), and (I) Urticaria (UA). The plots systematically exclude one genetic variant at a time to show that the statistical significance of the link is not too reliant on any individual variant. The vertical line in the center of each plot represents a lack of effect, while the position of the individual dots indicates the influence of removing each variant on the overall study. This approach offers valuable understanding regarding the consistency and dependability of the causal estimations, emphasizing the impact of EBNA-1 on these circumstances.

## 4. Discussion

For a considerable time, viruses have been observed to influence the clinical manifestations of various autoimmune diseases, including SLE, RA, and SS [1]. Viral infections trigger complex immunological responses aimed primarily at controlling the virus but can inadvertently initiate autoimmune reactions. Key mechanisms contributing to this include molecular mimicry, where viral antigens mimic host antigens, triggering immune responses that mistakenly target the body's tissues; bystander activation, where virus-induced inflammation activates immune cells that attack self-antigens; and epitope spreading, a process in which the immune response to viral antigens broadens to include self-antigens released during infection-related tissue damage [17]. These interactions highlight the intricate and often detrimental interplay between viral pathogens and the immune system, underscoring the need for a deeper understanding of these processes to reveal potential therapeutic targets and preventive strategies for autoimmune diseases.

EBV, a ubiquitous lymphocytic herpesvirus in the Human Herpesviruses (HHVs) family, is a large, enveloped DNA virus primarily transmitted through saliva, droplets, and other routes. It can initiate autoimmune diseases through molecular mimicry, particularly through its antigen EBNA1, which resembles host proteins, triggering autoimmune responses in genetically predisposed individuals. EBV latency III–transformed B cells play a crucial role during the promotion phase, acting as potent antigen-presenting cells. They not only produce inflammatory cytokines but also present viral and self-antigens, fueling autoreactive B and T cell proliferation. This dual role of EBV, as both initiator and promoter in the autoimmune cascade, underscores its significant contribution to the pathogenesis of various autoimmune diseases [18]. Moreover, EBV impairs the function of regulatory T cells, likely due to defects in $CD4^+$ $CD25^+$ cells, exacerbating immune dysregulation associated with autoimmune hepatitis [19].

In patients with RA, evidence suggests fragments targeting EBV antigen EBNA2 within anti-cyclic citrullinated peptide (anti-CCP) antibodies. Additionally, EBNA-2 is susceptible to cyclization by arginine deaminase [20]. In patients with SLE and EBNA-1, cross--reactivity occurs with SmB, SmD, RO, and dsDNA, fostering autoantibody production [21]. Patients with SS and prior, recent, or reactivated EBV infections exhibit significantly elevated levels of Th1 and Tfh 1 cells compared to those without active infection [22]. Traditional antivirals have limited effectiveness against EBV, mostly interfering with nucleic acid replication and reducing viral load. Nevertheless, infected cells persist, surface antigens endure, and EBV DNA integrated into cell nucleic acids remains present, yielding modest therapeutic effects. Hence, these approaches are considered insufficient. Another avenue involves a more aggressive strategy akin to lymphoma treatment, directly damaging infected cells, albeit with greater risks.

After cyclophosphamide treatment, patients with SLE have shown a reduction in EBV DNA copies, indicating similarities in treatment approaches. However, it remains unclear whether traditional antiviral therapy effectively diminishes viral load in plasma and impedes viral spread within the body. The focus on intracellular virus DNA copy numbers by infectious diseases departments contrasts with the common reliance on plasma-based tests in rheumatology, warranting further investigation.

The association between EBV infection and autoimmune diseases has been a longstanding subject of research [7]. EBNA-1 levels serve as a key marker for past infections. However, not all individuals infected with EBV develop autoimmune diseases. A meta-analysis by Robert et al. found no association between EBV seroprevalence and RA [23], likely due to the complex etiology of autoimmune diseases. Genetic factors such as MHC genes [24], ancestry [25], gene variants [26], and gender [27] play significant roles in the manifestation of these conditions. Additionally, other environmental factors including microorganisms (bacteria, viruses, and fungi [28], gut microbiota [29], smoking [30], and drugs (statins leading to immune-mediated necrotizing myopathy, non-steroidal

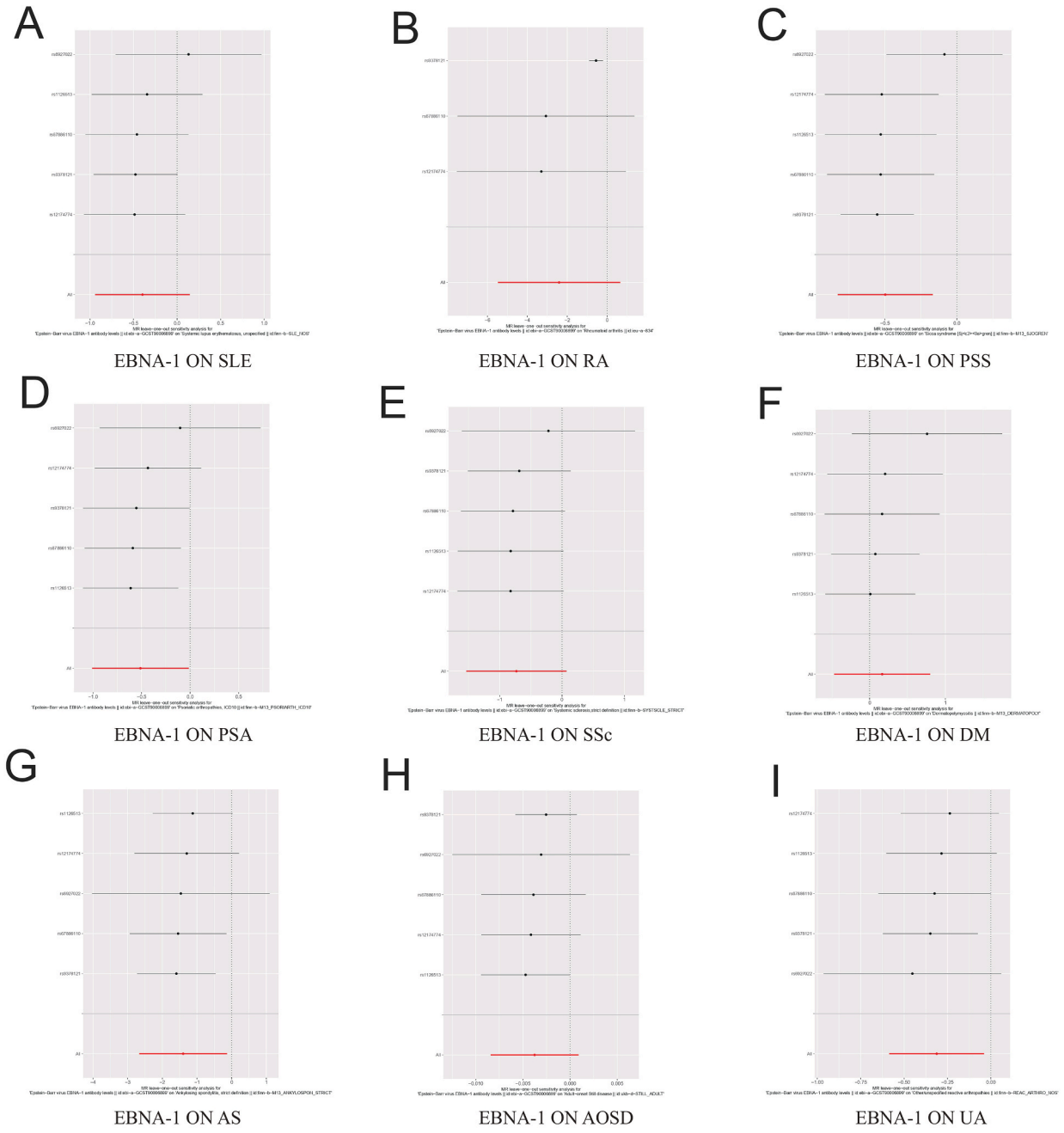


**Fig. 3.** Leave-one-out plot of MR Causality.

anti-inflammatory drugs to nephritis) also contribute substantially to the development and progression of autoimmune diseases.

Despite evidence linking EBV to various ARDs, debate surrounds whether EBV acts as a direct environmental trigger for these diseases. Additionally, antiviral treatments specific to EBV infection are lacking. This study aimed to investigate the potential causal role of EBV in ARDS through MR analysis. MR analysis leverages genetic variations that influence EBNA-1 antibody levels but do not directly affect ARD risk. We identified 3–5 such genetic variations (IVs) from GWAS on EBNA-1 antibody levels. Pleiotropy analysis did not reveal any significant confounding factors within most ARD GWAS datasets. Notably, three different MR analysis methods consistently demonstrated that these genetic IVs significantly influence ARD risk through their effect on EBNA-1 antibody levels, rather than through alternative pathways.

Our MR analysis reinforces the link between EBNA-1 antibodies and ARD risk. We found that genetically increased EBNA-1 levels significantly increased the risk of SS, UA, PsA, and AS. Each one standard deviation increase in EBNA-1 antibody blood levels corresponded to odds ratios of 0.61 (SS), 0.73 (UCA, 0.60 (PsA), and 0.25 (AS) for developing these conditions.

These outcomes were consistent across various MR methods, including MR-Egger, weighted median, and IVW analyses. Furthermore, our single-SNP and leave-one-out sensitivity analyses confirmed the robustness of our results, with no bias stemming from individual genetic variations. This study establishes a causal link between EBNA-1 antibody levels and multiple autoimmune diseases including SS, UA, PsA, and AS, using an MR approach. Our findings not only shed light on the role of EBV in these diseases but also demonstrate the applicability of MR in predicting relationships between pathogens and other diseases.

These insights hold significant implications for public health. They pave the way for developing preventive and therapeutic strategies for autoimmune conditions. Furthermore, this research provides a scientific basis for early identification and intervention in EBV-related complications, potentially reducing the global disease burden associated with this virus.

Prior studies linked elevated EBNA-1 antibody levels to ARDs [3]. However, these antibodies are often seen as markers of past EBV infections and are not treated. Currently, treatment for patients with ARDs and a history of EBV infection is limited, typically consisting in a short course of antiviral medications (e.g. one-week course of ganciclovir). Our research aims to contribute to future treatment strategies and elucidate the mechanisms underlying ARDs. Nonetheless, the impact of EB antibody levels on ARD relapse and progression, including their associated complications and genetic predisposition, remains unclear. Future studies using longitudinal multi-omics analyses, which integrate diverse types of data, might shed light on these uncertainties.

Future research requires interdisciplinary collaboration. Virologists and immunologists can offer mechanistic insights, data scientists can detect predictive signatures for targeted prevention, and clinicians can develop early interventions. This study has several strengths. Thus, we followed the three fundamental MR assumptions and used diverse methods to validate them. Incorporating GWAS data from individuals of European ancestry minimized population stratification. Furthermore, using independent statistical methods validated the effectiveness of 3–5 independent genetic variants as IVs. The consistency of the results across various MR analysis methods, encompassing MR-Egger, weighted median, and IVW, strongly supports a causal association between EBNA-1 antibody levels and the risk of SS, UA, PsA, and AS.

Nevertheless, this study is not without limitations. It primarily focuses on individuals of European ancestry which limits the generalizability of the findings to other populations. Additionally, the effective IVs are limited to 3–5 genetic variants. Heterogeneity in our analyses highlights the need for further research in broader populations and the application of even stricter MR methodologies to strengthen the causal link between EBNA-1 and autoimmune diseases.

## 5. Conclusion

In summary, we employed an MR framework to analyze lifelong exposure to EBV through EBNA-1 antibody levels. Our study provides robust evidence of a causal association between higher levels of EBNA-1 antibodies and an increased risk of developing several ARDs. More precisely, we found that individuals with genetically determined higher EBNA-1 levels had a greater risk of PSS, PSA, AS, and UA.

## Availability of data and material

All relevant data are within the paper.

## Data availability statement

The datasets presented in this study come from IEU OpenGWAS (https://gwas.mrcieu.ac.uk/) are available for free download. Further inquiries can be directed to the corresponding authors.

## CRediT authorship contribution statement

**Jinjiao Li:** Writing – original draft, Software, Formal analysis, Data curation, Conceptualization. **Bao Li:** Supervision, Software, Data curation.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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